EXHIBIT 1
PART 1 OF 2

11/14/2002

GlaxoSmithKline
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Tel. 919 483 2100
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COVER LETTER VIA FACSIMILE TRANSMISSION (301) 594-6771
FOLLOWED BY AIRBORNE EXPRESS with ATTACHMENTS

November 14, 2002

Lesley R. Frank, Ph.D., J.D.
Regulatory Counsel
Food and Drug Administration
Division of Drug Marketing,
Advertising and Communications
HFD-42, Rm. 8B—46
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-358
Wellbutrin SR (bupropion HCl) Sustained-Release Tablets
MACMIS #11170

Dear Dr. Frank:

As previously discussed, we are submitting information in response to FDA's letter of October 9, 2002, on a rolling basis. As our first submission, we enclose documents in response to request number 5:

5. Please provide copies of all slides, videos, handouts, manuals, agendas, outlines, brochures, prepared statements, proposed or suggested answers to questions, points for emphasis, studies, reports, reprints, background information, instructions, guidelines, FAQs, computer media, questionnaires, or other materials (a) presented or distributed at or in connection with any program, seminar, discussion, conference or other presentation....or any of the individuals or entities identified in item 3 above relating to Wellbutrin SR; ...(c) provided or shown to, or discussed with, physicians, or other healthcare professionals, during or for the purposes of any speaker training programs relating to Wellbutrin SR.

GSK Confidential/Proprietary
Submitted to FDA
MACMIS #11170

WN 0004904

GSK's response

As a partial response to this request, GSK is providing materials from two speaker training programs for Wellbutrin SR® held since January 1, 2001: (1) P.R.I.D.E. 2001 Speaker Training Program for Wellbutrin SR, January 26-28, 2001, and (2) P.R.I.D.E. 2002 Speaker Training Program for Wellbutrin SR, December 6-7, 2001.

Appendix A consists of templates of the correspondence sent by GSK to attendees of GSK's P.R.I.D.E. 2001 Speaker Training Program and the notebook provided to attendees at this meeting. The templates include:

- Invitation letter
- Participant Information Form
- Participant Confirmation
- Important Meeting Information
- Glaxo Wellcome Speaker Event Member Profile Form
- National Speaker Agreement
- Regional Speaker Agreement
- Welcome letter

Appendix B consists of templates of the correspondence sent by GSK to attendees of GSK's P.R.I.D.E. 2002 Speaker Training Program and the notebook provided to attendees at this meeting. The templates include:

- Invitation letter
- Registration Form
- Preliminary Program Agenda
- National Speaker Agreement
- Regional Speaker Agreement
- Program Participant welcome letter with attached Agenda
- Program information Sheet

Attendees at these two programs were required by Company policy to contract with GSK both to attend the program, and become a speaker on behalf of GSK for its P.R.I.D.E. programs for the following year. Also, please note that Drs. Ryan and Anderson did not participate in either of these two programs, either as faculty presenters or attendees. Dr. Wolkowitz was an attendee at the January 2001 program.

Please note that all materials and information provided in response to your requests and marked "GSK Confidential/Proprietary" are confidential and proprietary to GSK, and as such, are protected under the applicable provisions of 18 U.S.C. 1905 or 21 U.S.C., Section 331(j), and all accompanying regulations. Additionally, GSK is providing all information and documents to the Division of Drug Marketing, Advertising and Communications for its use during this inquiry only.

Sincerely,

Lauren C. Stevens
Vice President and
Associate General Counsel
US Legal Operations

Enclosures: Appendices A and B

12/23/2002

GlaxoSmithKline

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COVER LETTER VIA FACSIMILE TRANSMISSION (301) 594-6771
FOLLOWED BY AIRBORNE EXPRESS with ATTACHMENTS

December 23, 2002

Lesley R. Frank, Ph.D., J.D.
Regulatory Counsel
Food and Drug Administration
Division of Drug Marketing,
Advertising and Communications
HFD-42, Rm. 8B—46
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-358
Wellbutrin SR® (bupropion HCl) Sustained-Release Tablets
MACMIS #11170

Dear Dr. Frank:

This represents a supplemental response to your letter of October 9, 2002, concerning Wellbutrin SR (bupropion HCl) Sustained-Release Tablets. We are providing information and documentation responsive to Requests 14 and 15. We are also supplementing our response to Request No. 5 by providing additional, responsive material.

Consistent with our prior agreement, reflected in our letter of October 29, the information provided herein and responsive to your requests covers the period January 1, 2001 through October 9, 2002. We refer to this period below as the "relevant time period."

Request No. 14

With respect to the "Speaker Training Slides for Wellbutrin SR" dated December 2001:

a. describe the purpose and usages for these slides;
b. identify all persons who participated in the preparation, revision, supervision and approval of these slides;

c. identify each presentation or event at which these slides were shown, presented, or otherwise used at which persons not employed by GSK were present; describe the purpose of such presentation or event, and identify the number and nature of the attendees at such event;
d. describe any distribution of these slides to any person or entity outside of GSK;
e. provide any other versions of this presentation, and any handouts, notes, manuals, instructions, or other materials used in conjunction with these slides at any event or presentation.

GSK's Response

Before responding to the specific questions posed in Request No. 14, we believe it would be useful to provide background information regarding GSK's speaker meeting programs and GSK's requirements for its trained speakers. GSK uses speaker training meetings as an opportunity to educate and train a core group of national and local healthcare professionals (hereinafter "Faculty") on data and information for a GSK product so that the Faculty can deliver effective presentations on the product when asked to speak by the Company. GSK requires all Faculty who attend the meeting to sign an agreement. One purpose of the agreement is to secure a clear understanding with the Faculty that when they speak on behalf of GSK, their affirmative presentation must be confined to a discussion of FDA-approved uses for the product. (As an example, we included the template of the agreement signed by the Faculty for the December 2001 program in Appendix B of our November 14, 2002 submission.) In addition to the provision in the speaker training agreement, a similar requirement is included in the Speaker Bureau Member Profile form/contract. (See Appendices A, B and C.) This requirement is again re-emphasized during the opening presentation of the speaker training meeting.

During the speaker training meeting, clinical data is presented by healthcare professionals to further educate the Faculty about the specific disease area, as well as treatment interventions in the disease state with a focus on the GSK product. Training at the meeting is generally focused on data concerning approved uses of the GSK product. GSK may also share with the Faculty limited data concerning off-label uses. The purpose of sharing off-label information is to keep Faculty educated and informed of recent clinical data relating to the product. This information assists them in responding appropriately and accurately to unsolicited questions posed during their presentations. It is important to understand that prior to discussions of off-label information during training meetings, GSK emphasizes that such information (a) may not be presented by the Faculty during affirmative presentations, (b) is being included in the training meeting solely for the purpose of keeping the Faculty educated and updated about the product, and (c) may only be used to assist the Faculty in responding to unsolicited questions directed at Faculty during presentations. Moreover, although slides containing off-label information may be shown at a speaker

training meeting, presentation-ready slides of the off-label content are not provided to Faculty at these training meetings. The meeting slides are provided only to Faculty who make an unsolicited request for the slides, and the slides are sent to them only after the meeting.

In preparation for the December 2001 Speaker Training Meeting, GSK developed slides that would be used by the presenters at the meeting during their presentations. These slides underwent an internal review by GSK's medical, legal and regulatory personnel. The following GSK personnel were involved in the development and review of the content of the slides shown at the December 2001 Speaker Training program:

Dawn Childs, Brand Marketing, Wellbutrin SR
Jack Modell, M.D., Clinical Development and Medical Affairs
Carol Rockett, Pharm.D., Clinical Development and Medical Affairs
Barbara Haight, Pharm.D., Clinical Development and Medical Affairs
Helen Smawley, Pharm.D., Clinical Development and Medical Affairs
Sherrie Shade, J.D., Senior Counsel, U.S. Legal Operations
James E. Murray, Vice President, US Regulatory Affairs

Non-GSK person involved in the development of certain slides shown at the December 2001 Speaker Training program included:

Ken Fujioka, M.D. (depression and obesity slides)

The overall purpose of these slide presentations was to provide the Faculty being trained with information regarding Wellbutrin SR so that they could participate as speakers in GSK's P.R.I.D.E. program for Wellbutrin SR.[1] The primary objective of the P.R.I.D.E. program is to educate practicing primary care physicians about the appropriate role of Wellbutrin SR in the treatment of depression. The majority of the slides presented at the speaker training meeting contained on-label information about Wellbutrin SR that trained Faculty can affirmatively discuss in their presentations for GSK. GSK also created some slides showing off-label information to educate and inform the trained Faculty about the most recent data on Wellbutrin SR, and prepare them to answer unsolicited questions during their own GSK-sponsored presentations.

Due to the complex nature of depression, and its numerous causes and effects, it is important that treating physicians understand and recognize the potential physiologic and other changes that may occur as a result of depression or treating patients with anti-depressants, including Wellbutrin SR. For example, because weight gain or loss is often a significant issue in depressed patients and with patients undergoing treatment for depression, physicians generally are

[1] P.R.I.D.E. is the acronym for "Peer Review of Intimacy Depression and Efficacy." We will provide a more detailed description of the P.R.I.D.E. program in a future supplemental submission in response to Request No. 1 which seeks a description of GSK's speaker programs and related activities for Wellbutrin SR. We also will be providing you specific data regarding P.R.I.D.E. such as program dates, locations, speakers, speaker compensation and expenses in response to Requests 3 and 4.

mindful of the potential effect of anti-depressant therapy on weight-gain or weight-loss. GSK's data for Wellbutrin SR and its effect on weight were shared with the Faculty so that they would have an understanding of these data if questioned during a GSK-sponsored presentation.

At the December 2001 meeting, Faculty received a notebook containing a paper copy of the slides used during the meeting's presentations. (A paper copy of all of the slides shown at the meeting is contained in the notebook for this program that we submitted to you on November 14, 2002.) The notebook is formatted to allow the Faculty to follow along with the speaker's presentation, and take notes as desired. No presentation-ready slides were provided to the Faculty at the meeting. During the meeting, approximately 20 Faculty asked the on-site GSK Medical Affairs representative to send to them the actual slides shown during the meeting.

After the December 2001 speaker training meeting, GSK's Medical Information department created a shortened version of the presented slide set, by eliminating most of the business-oriented and individual presenter introduction slides (hereinafter referred to as "Abbreviated WBSR STP Slides"). (Note: Medical Information fulfilled unsolicited requests for these slides in CD-ROM format with the label: "Speaker Training Slides for Wellbutrin SR December 2001.") GSK personnel involved in the development of Abbreviated WBSR STP Slides included:

Dawn Clines, Pharm.D., Clinical Development and Medical Affairs
Melinda Mitton, Pharm.D., Clinical Development and Medical Affairs
Helen Smawley, Pharm.D., Clinical Development and Medical Affairs

There are four versions of Abbreviated WBSR STP Slides identified by date[2] and attached as follows:

Version	Appendix
Abbreviated WBSR STP Slides (01/02/02)	D
Abbreviated WBSR STP Slides (2/25/02)	E
Abbreviated WBSR STP Slides (5/17/02)	F
Abbreviated WBSR STP Slides (9/6/02)	G
Abbreviated WBSR STP Slides 10/31/02	H

The differing versions reflect updates made by GSK's Medical Information Department to Abbreviated WBSR STP Slides. (None of the revisions related to any data regarding Wellbutrin SR and weight loss.) Many of the revisions were minor or editorial in nature. One of the more significant revisions was an update in the 2/25/02 version of this slide set that added information about a new

[2] As the slide sets are updated, Medical Information uses the most recent version to respond to any unsolicited requests for the particular slides.

contraindication to the approved labeling for Wellbutrin SR. (see slide 71, Appendix F) The revised slide set became Abbreviated WBSR STP Slides (05/17/02).

Abbreviated WBSR STP Slides (9/6/02) reflects a change in GSK's position regarding Medical information's response to unsolicited requests from physicians who request slides from the Company, and the use of the "§" symbol on these slides. Prior to this time, GSK's Medical Information department provided physicians who requested slide sets that included both on and off-label information, slide sets with certain slides marked with a "§" symbol. GSK used this symbol to let the physician know that the information on the particular slide was not appropriate for use in GSK-sponsored presentations. (In general, the symbol reflected that the data were considered "off-label" information.) However, sometime in mid-2002, Medical Affairs began placing this symbol on all slides in slide sets containing any off-label information as a means to inform requesting physicians that the slide set, itself, was not intended for use as a slide lecture kit in GSK-sponsored speaker presentations. Therefore, you will note in your review of Abbreviated WBSR STP Slides (9/06/02) that all of the slides contain the "§" symbol. The inclusion of the "§" symbol on all slides in that version, however, does not indicate or suggest that such information depicts off-label or unapproved uses. It merely means that this particular slide set is not authorized or approved for affirmative presentations.

In approximately January 2002, GSK's Medical Information Department fulfilled the unsolicited requests for slides from the Faculty at the December 2001 speaker training meeting with Abbreviated WBSR STP Slides (01/02/02) in CD-ROM format entitled "Speaker Training Slides for Wellbutrin SR December 2001" (In your October 9, 2002 letter, we believe that you refer to a version of this CD-ROM as "Speaker Training Slides for Wellbutrin SR dated December 2001.") GSK's Medical Information Department also sent this CD-ROM to other healthcare professionals submitting unsolicited requests for these slides. GSK policy permits fulfillment of such unsolicited requests for slides.

During the development of our response to your letter of October 9, 2002, we also determined that Abbreviated WBSR STP Slides were used for regional speaker training. Because many of the physicians invited to the December 2001 speaker training meeting declined to attend due to their concerns over discretionary air travel after the events of September 11, 2001, GSK Regional Medical Scientists ("RMS's") trained additional speakers in one-on-one or small group settings. RMS's are medical professionals who are independent of the GSK sales/marketing organization and report into GSK Clinical Development & Medical Affairs – North America. They provide regional support for GSK's Medical Information Department. They are regionally based throughout the U.S. and assist the Medical Information Department by providing locally based medical-support to healthcare professionals upon request.

The RMS's trained approximately 160 healthcare professionals ("physician/trainees") from January through September 2002.[3] They showed the physician/trainees a presentation created specifically for this training entitled "Speaker Training Update 2002 Wellbutrin SR." (Appendix I) This presentation was comprised mainly of on-label information. However some off-label data were shown to the physician/trainees. This slide presentation was not left with the physician/trainees. Physician/trainees were not paid for this training and GSK required that they sign an agreement for the training similar to the agreement used at speaker training programs. (Appendix J) The agreement included a provision requiring physician/trainees to confine their GSK-sponsored presentations to on-label information about GSK products. (See paragraph 3 in the agreement.) Additionally, RMS's reviewed the following information contained on slide 78 of the slide presentation they showed to the physician/trainees:

> **As a reminder, the program and content of your discussion and any materials shown to or disseminated to the audience will be considered by the FDA to be a promotional message from GSK, which is subject to FDA regulation. Therefore, except when responding to unsolicited questions, please confine your discussion about pharmaceutical products and materials about such products, to information consistent with and not outside of, the currently approved package inserts for the product. Further, your discussion and materials must include a balanced presentation of the adverse events, contraindications, warnings, precautions, and other appropriate safety-related information for the products.**

After the RMS training, the RMS's should have provided the physician/trainees with a slide lecture kit intended for their use in non-independent presentations for GSK. However, the RMS's believed that Abbreviated WBSR STP Slides was the slide lecture kit that they were to provide the physician/trainees for this purpose. Consequently, the RMS's either gave, or requested that Abbreviated WBSR STP Slides (in CD-ROM format) be sent to the physician/trainees for use in their future GSK-sponsored presentations. It is important to note, however, that consistent with the physician/trainees' agreement, and the information on Slide 78 above, the second slide in Abbreviated WBSR STP Slides reminds the physician/trainees that information designated by a "§" symbol is not to be used in affirmative presentations sponsored by GSK.

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[3] GSK policy allows RMS's, on an infrequent basis, to train individual physicians as speakers for GSK. These physicians must register with the Speakers Bureau before giving presentations for GSK. The RMS can review the product's approved slide kit (i.e., the slide kit submitted to FDA on Form 2253) with the physician and GSK can use the physician to deliver presentations. In the situation described herein, the RMS's were permitted to share on-label and a smaller percentage of off-label information for Wellbutrin SR with these physicians since many of them would have attended the December 2001 meeting absent the extenuating circumstances of 9/11.

Since learning that Abbreviated WBSR STP Slides has been provided to the RMS-trained physicians for use at GSK-sponsored, non-independent events, we have taken the following steps to ensure that all RMS-trained physicians understand they should not use Abbreviated WBSR STP Slides when they speak at GSK-sponsored, non-independent presentations:

1. Physicians are being personally contacted by the RMS's to inform them not to use Abbreviated WBSR STP Slides when they speak on behalf of GSK.
2. A letter has been sent to these physicians informing them and advising against the use of Abbreviated WBSR STP Slides in GSK-sponsored presentations. (Appendix K) Also, enclosed with the letter is a CD-ROM containing a slide lecture kit for Wellbutrin SR for use at GSK-sponsored non-independent presentations. (Appendix L)
3. A RMS will talk with each physician in more detail to confirm receipt of the letter and replacement slide lecture kit, and to gather information concerning any use or distribution of Abbreviated WBSR STP Slides at GSK-sponsored non-independent presentations.
4. GSK's internal procedures are being revised to ensure there is a clear communication and documentation within all groups involved in slide development and distribution of which slide sets are appropriate for use by GSK-sponsored speakers at non-independent speaker programs.

We have asked the RMS's to complete this task on or before January 10, 2003. To the extent that these activities produce additional, responsive information, we will supplement our response to Request No. 14 with such information.

Request Number 15

Several slides contained in the "Speaker training Slides for Wellbutrin SR: dated December 2001 contain comparisons of Wellbutrin SR to Zoloft, Paxil, and Prozac (see, for example, slides nos., 89, 90, and 91). For each such slide, identify and describe the studies or other evidence supporting the comparison depicted in the slide, and provide copies of any studies, articles, or other materials in support hereof.

GSK's Response

Appendix M contains the requested studies, articles and other evidence supporting the presentations depicted in these slides. We are using Abbreviated WBSR STP Slides (5/17/02). Appendix M is organized as follows:

- A complete set of the 93 slides copied from Abbreviated WBSR STP Slides (5/17/02) (We have added slide numbers for ease of reference)
- Tabs for each comparative slide (the tab label references the slide number)
- Behind each tab is:
  (1) A description of the slide and the data supporting the information shown on the slide;
  (2) A full page color copy of the slide; and
  (3) The supporting data document(s).

GSK's Supplemental Response to Request No. 5

In our prior response of November 14, 2002, we enclosed materials that had been provided to those attending the January and December 2001 speaker training meetings. Following that submission, we have obtained additional material and documentation provided to meeting attendees that is responsive to Request No. 5. Therefore, we are supplementing our response by providing you the following materials:

January 26-28, 2001 Speaker Training Meeting (Appendix N)

1. Template invitation to National Speakers
2. Attendee Welcome Package (Schedule of Events, Participant List, Working Dinner Invitation and Saturday Celebration Dinner)
3. Poster Book containing posters presented at the meeting
4. Speaking/Facilitator Preferences

December 6-7, 2001 Speaker Training Meeting (Appendix O)

1. Template invitation
2. Template confirmation letter

The representations made in this response are based on our information and belief. If we become aware of additional or new information that materially alters the accuracy of these responses, we will supplement these responses.

Please note that all materials and information provided in response to your requests and marked "GSK Confidential/Proprietary" are confidential and proprietary to GSK, and as such, are protected under the applicable provisions of 18 U.S.C. 1905 or 21 U.S.C., Section 331(j), and all accompanying regulations. Additionally, GSK is providing all information and documents to the Division of Drug Marketing, Advertising and Communications for its use during this inquiry only.

Sincerely,

Lauren C. Stevens
Vice President and
Associate General Counsel
US Legal Operations

Enclosures: Appendices A through O

2/28/2003

D07521347 514

GlaxoSmithKline

Cover Letter Via Facsimile Transmission (301) 594-6771
Followed By Airborne Express with Attachments

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February 28, 2003

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Re: NDA 20-358
Wellbutrin SR® (bupropion HCl) Sustained-Release Tablets
MACMIS #11170

Dear Dr. Frank:

This letter represents a supplemental response to your letter dated October 9, 2002, concerning Wellbutrin SR (bupropion HCl) Sustained-Release Tablets. We are providing information and documentation responsive to Requests 1 and 12, as well as narratives regarding Dr. Anderson and Dr. Ryan that are responsive to multiple requests.

Consistent with our prior agreement, reflected in our letter of October 29, 2002, the information provided herein and responsive to your requests covers the period January 1, 2001 through October 9, 2002. We refer to this period below as the "relevant time period."

Request No. 1

Please describe GlaxoSmithKline's (GSK's) plans, programs, and activities relating to the use of programs, speakers, speakers bureaus, seminars, luncheons, roundtables, satellite, telephone, video, or internet broadcasts, and other similar presentations to physicians or other professionals for Wellbutrin SR. Please describe any discussion, presentation, prepared responses, or other treatment or activities relating to use of Wellbutrin SR for weight loss included therein.

GSK's Response to Request No. 1

A. Introduction

GSK has developed and established programs, presentations and other activities designed to educate and inform physicians and other health care professionals about the clinical management of depression and the use of Wellbutrin SR. GSK has educated physicians through promotional material such as detail aids, brochures, and videos, all of which the Company has submitted to FDA as 2253-material. GSK's educational activities also include employing national and local health care professionals ("speakers") to deliver scientifically relevant presentations relating to depression generally, treatment options, and the use of Wellbutrin SR. The speakers are members of GSK's Speaker's Bureau. The speakers typically deliver presentations during luncheons, roundtables, dinner meetings, and teleconferences. With the exception of promotional videos and internet websites, GSK has not delivered presentations to health care professionals on Wellbutrin SR through satellite, video, or internet broadcasts. We describe GSK's specific programs and activities for Wellbutrin SR in greater detail below.

As you review and evaluate GSK's programs and activities for Wellbutrin SR, it is important that you remain mindful of the following. First, you will notice that some -- but not all -- of the programs and activities described below have a promotional component or are otherwise focused on Wellbutrin SR. We understand Request No. 1 seeks a description of (a) activities that are part of GSK's effort to promote Wellbutrin SR, and (b) activities or events that are non-promotional, independent, and unrelated to marketing and sales. Therefore, we have included a description of Wellbutrin SR speaker training and speaker events. We have also included a description of GSK's independent medical education activities even though they are not dedicated to Wellbutrin SR; GSK does not control or influence the content of these educational programs, hence, they are not promotional in nature. Similarly, we have also included a description of the advisory boards GSK has convened for Wellbutrin SR, another non-promotional activity. The Boards are designed to bring leading national and local physicians together so that GSK may obtain advice and feedback from these consultants on a variety of issues, including depression, clinical studies, and other issues relating to Wellbutrin SR.

Second, we understand from your October 9, 2002 letter that this routine inquiry focuses on whether GSK has engaged in the promotion of Wellbutrin SR for weight loss or as a treatment for obesity. We recognize that the product has not been approved for those indications and may not be promoted for those uses. Indeed, GSK has not developed, devised, established, or maintained any program or activity to promote or encourage, either directly or indirectly, the use of Wellbutrin SR as a means to achieve weight loss or treat obesity. Wellbutrin SR is an effective first-line agent for the treatment of depression with a low incidence of sexual dysfunction and weight gain.

GSK's promotional material and activities for Wellbutrin SR are consistent with the approved Prescribing Information and the supporting clinical data. For example, affirmatively representing that there is a low incidence of weight gain associated with the product is warranted by, and entirely consistent with, the FDA-approved Prescribing Information. *See* Prescribing Information, Precautions, Table 2: Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials. In addition, the Precautions section states that fewer patients may experience weight gain taking the immediate release form of bupropion than with other antidepressant products, and that physicians should consider the weight-reducing potential of Wellbutrin SR when prescribing the product:

> In studies conducted with the immediate-release formulation of bupropion, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of Wellbutrin SR Tablets should be considered.

Educating psychiatrists and primary care physicians about the weight loss potential associated with Wellbutrin SR is important to ensure that physicians appropriately prescribe the product in depressed patients and consider weight changes. Indeed, both the precaution for Wellbutrin SR cited above and the DSM-IV criteria for a major depressive episode confirm the importance of considering weight and weight changes when diagnosing and treating depression. To educate physicians about weight loss potential and to prompt consideration of those consequences, GSK's P.R.I.D.E. ("Peer Review of Intimacy, Depression, and Efficacy") Speaker Training slides contain information about weight loss associated with Wellbutrin SR. Importantly, however, the training materials do not promote Wellbutrin SR for weight loss or obesity. As noted, GSK has not developed or maintained promotional plans or activities to directly or indirectly promote Wellbutrin SR for weight loss or the treatment of obesity.

B. <u>Speaker Training Programs – P.R.I.D.E. & Regional Training</u>

The P.R.I.D.E. program is a two-part program where selected physicians, typically psychiatrists and primary care physicians, are trained to speak about Wellbutrin SR. After physicians successfully complete the training program, they become eligible to deliver presentations at P.R.I.D.E. speaker events. The objective of the P.R.I.D.E. program is to educate physicians about the treatment of depression and the appropriate use of Wellbutrin SR as an effective first-line agent for the treatment of depression.

During the relevant period, GSK trained selected physicians to speak about Wellbutrin SR through two programs – P.R.I.D.E. and regional training conducted by Regional Medical Scientists ("RMS"). GSK has hosted two P.R.I.D.E. Speaker Training programs – one during January 26-28, 2001, the second during December 6-7, 2001. In our initial response, dated November 14, 2002, we provided the material related to both P.R.I.D.E. Speaker Training programs. *See* Letter of November 14, 2002 at 2, and

Appendices A & B thereto. Two hundred twenty-five (225) physicians attended the January 2001 P.R.I.D.E. training program, and 78 attended the December 2001 training program. Of the 78 attendees at the December 2001 training, 41 had also attended the January 2001 training program. The remaining 37 attendees were undergoing P.R.I.D.E. training for the first time.

GSK's second program for training physicians on Wellbutrin SR was provided on a regional and periodic basis throughout 2002. GSK initiated this program to train interested physicians because many physicians were unable to attend the P.R.I.D.E. Speaker Training Program in December 2001 due to travel and other concerns that surfaced in the wake of the September 11, 2001 terrorist attacks. This regional training was conducted at various times and locations during 2002 by a GSK Regional Medical Scientist.

RMS's are medical professionals, typically holding a degree in medicine, pharmacy, or a doctorate in a medical specialty. A minimum of eight years of clinical practice and/or pharmaceutical industry experience is required for the position. RMS's provide regional clinical, medical, and scientific support for GSK's Medical Information Department. Some of their other key responsibilities include developing credible medical and scientific expertise to support physicians and key opinion leaders on a national, regional, and local basis; addressing medical, scientific, and pharmacoeconomic issues related to GSK products; and providing training to potential speakers. Essentially, RMS's are scientists operating in a similar capacity as Medical Information Scientists within GSK except their activities are performed in the field. RMS's are independent of GSK's sales and marketing organizations; they are part of, and report into GSK's Clinical Development & Medical Affairs – North America. Compensation to RMS's is not based on sales of GSK products.

Typically, the RMS's conducted the training in their regions in small groups of fewer than 10 physicians. The physicians were not compensated for attending the training, and the RMS's were not provided additional compensation for conducting this training. From January through September 2002, 169 physicians were trained under this program.[1]

Between January 1, 2001 and October 9, 2002, GSK trained a total of 382 physicians through the P.R.I.D.E. Program Speakers Training and RMS regional training. As described in greater detail in response to Request No. 12, 342 (89.5%) of

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[1] Of the 169 RMS-trained physicians, 120 had not attended P.R.I.D.E. training in either January or December 2001; the remaining 49 had attended either one (or both) of the P.R.I.D.E. training programs. We provide additional information about the RMS training process in our supplemental response dated December 23, 2002, at 5-6, and our response to Request No. 12, below. The information presented above, our response to Request No. 12, and the information provided in our December 23 letter addresses the questions you and your colleagues raised about the RMS training during our teleconference on January 22, 2003.

these physicians have delivered at least one presentation on Wellbutrin SR during the relevant period.

C. Enrollment in the GSK Speakers Bureau

Before health care professionals are eligible to speak on behalf of GSK, they are required to become members of the GSK Speakers Bureau. To become a member, the speaker is required to complete a contract and an IRS W-9 form. (For contract templates, *see* GSK's response letter of December 23, 2002, at 2, and Appendices A, B & C, thereto.) The contract informs speakers about the requirements, conditions, and policies associated with delivering presentations on behalf of GSK. It specifically notifies speakers of GSK's policy that any presentations on behalf of the Company must be consistent with the currently approved package insert for any pharmaceutical product discussed during the presentation. This notice is reflected in the following contract provision.

> **Compliance with FDA Regulations and Guidance.** You may have received a slide kit from GSK to assist in making these presentations. When GSK asks you and you agree to speak at a promotional program, please understand that the program and the content of your discussion and any materials shown to or disseminated to the audience will be considered by the FDA to be a promotional message from GSK, which is subject to FDA regulation. Therefore, *except when responding to unsolicited questions*, please confine your discussion about pharmaceutical products (whether manufactured by GSK or any other company) and materials concerning such products, to information consistent with and not outside of, the currently approved package insert for the product. If you discuss your clinical experience with any product, please describe it as that. Your discussion and materials must include a balanced presentation of the adverse events, contraindications, warnings, precautions, and other appropriate safety-related information for the products as well as appropriate information related to any limitations on the efficacy or use of the products. Do not make any comparative claims between products that are not supported by substantial scientific evidence.

See, e.g., GSK Response, dated December 23, 2002, Appendix C thereto, Section 3 (Bates No. WN-0005194).

For those attending the P.R.I.D.E. speaker training programs either in January or December 2001, GSK required all attendees to complete the required forms and contract in order to participate in the training program. Copies of the contracts and forms used during the P.R.I.D.E. training programs were provided to you in our

November 14, 2002 submission in Appendices A and B. Shortly after these training programs, GSK enrolled the attending physicians into GSK's Speakers Bureau.

Physicians who participated in the RMS training were not paid to attend this training, and GSK required that they sign an agreement for the training similar to the agreement used at speaker training programs. However, the process of enrolling these physicians in the GSK Speakers Bureau differed in that GSK did not require the attendees to complete the required Speakers Bureau forms during the RMS training program. After undergoing RMS training, the physicians were enrolled in the Speakers Bureau, if they were not already members, when a GSK sales representative asked the physician to lecture at a specific speaker event. Therefore, when the sales representative asked the physician to speak, and entered a non-independent GSK program into GSK's system for speaker programs with the particular physician designated as the speaker, GSK Speaker Events staff would be prompted to determine whether the physician is a member of the Speakers Bureau. If the physician was not currently a member, then Speaker Events staff would send the physician the requisite forms for completion before becoming a member and before the program is conducted. This process was followed for all of the RMS-trained physicians not already members of the GSK Speakers Bureau who have delivered at least one presentation on Wellbutrin SR.

Because it is impractical and unduly burdensome, GSK, like other members of the pharmaceutical industry, does not require physicians to attend speaker training as a prerequisite to enrollment in its Speakers Bureau. Consequently, GSK has enrolled physicians into its Speakers Bureau who did not receive P.R.I.D.E. or RMS training on Wellbutrin SR. However, each of the physicians that GSK enrolled was required to complete the required forms and enter into the contract described above.

D. Speaker Program Events

P.R.I.D.E. speaker events include "live events," such as dinner meetings, and teleconferences directed at providing lectures that educate psychiatrists and primary care physicians about Wellbutrin SR. GSK sales representatives are responsible for selecting the venue, date, and time, identifying a speaker, preparing an invitation list, and selecting a topic from a list of six established topics.[2] GSK contracts with a third party, SCS Healthcare Marketing, to coordinate the events and handle the related administrative duties.

In addition to the P.R.I.D.E. speaker events, GSK pharmaceutical sales representatives arrange and host speaking events where health care professionals, usually physicians, are invited to speak to other health care professionals about

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[2] The six established topics are: (1) Choosing an Antidepressant for the Long Haul; (2) Using Wellbutrin SR® in the Primary Care Setting; (3) Depression, Antidepressants, and Sexual Dysfunction; (4) Depression and Intimacy: Strategies for Discussing Sexual Dysfunction with Patients; (5) Issues in the Management of Depression; and (6) Options for the Primary Care Treatment of Depression.

Wellbutrin SR. This usually occurs in a lunch or dinner setting. GSK sales representatives are responsible for coordinating the venue, date, and time, identifying a speaker, and preparing an invitation list. Physicians that speak at these events are not required to attend the P.R.I.D.E. Speaker Training or other formal training, although some have received such training. As noted above, prior to the presentation, the speaker is required to become a member of GSK's Speakers Bureau and sign a contract agreeing to comply with certain GSK policies and FDA requirements. The speaker is compensated for delivering the lecture.

In 2001, GSK sponsored approximately 830 P.R.I.D.E. speaker events, and 3000 other speaker events relating to Wellbutrin SR. From January 1, 2002 through October 9, 2002, GSK sponsored approximately 1850 P.R.I.D.E. speaker events, and 2800 additional speaker events relating to Wellbutrin SR. In our next submission, we will provide the databases listing all speaker events including the date, location, speaker, and where available, the number of attendees.

E. **Independent Medical Education**

GSK periodically sponsors independent medical education through (1) unrestricted grants to institutions and associations that support independent symposia or Continuing Medical Education ("CME") events, and (2) independent companies and vendors contracted by GSK to coordinate and administer independent activities or programs. GSK does not participate in the development of these programs, or influence or control their content.

By way of example, in May 2002, GSK sponsored an American Psychiatric Association ("APA") Symposium on Women's Health in Philadelphia, Pennsylvania, titled, "Chronic Episodic Disorders: Comorbidity and Comprehensive Integrated Treatment." The program was developed for psychiatrists to increase their awareness of the changing mental health needs of a woman throughout her life. After the APA approved the program and selected the program speakers, it published the program topic to members of the pharmaceutical industry for the purpose of determining which companies were interested in providing financial support. GSK subsequently decided to provide an unrestricted educational grant to APA and contracted with a third party, Synergy Communications, to administer the program. There was no promotional aspect to this program. Moreover, GSK did not participate in the development of the program, or influence or control its content. Similarly, GSK sponsored a CME program during the May 2001 annual APA meeting. That program, also sponsored through an unrestricted educational grant, was selected by the APA and titled, "Issues in the Long-Term Treatment of Depression."

During the relevant time period, GSK sponsored additional independent medical education programs, namely Continuing Medical Education ("CME") Express, and Medical World Conference education. Both of these were independent, industry-

sponsored CME programs administered by a third party. These programs offer physicians flexibility to earn CME credits in a time-frame suited to their schedules.

The typical CME Express program educates approximately five (5) primary care physicians about depression-related disorders through short 30-minute speaker presentations over lunch. Attendees receive a one-half CME credit and complimentary lunch. As an independent, industry-sponsored CME program, GSK provided an unrestricted educational grant to fund the program, but did not control the content of the presentations. Instead, a third-party administrator, Primary Care Network ("PCN"), a non-profit, tax exempt organization, owns and implements CME Express pursuant to an independent agreement with GSK. PCN determines which physicians present at the CME program and coordinates the speaker module directly with the physician. PCN also extends approximately 25 invitations to each pre-selected geographical area, and GSK may supplement these invitations. PCN accepts invitees on a first-come, first-served basis.

The Saturday Symposia programs took place from March through September 2002, and were titled, "Understanding Depression: Matching the Neurotransmitter to the Patient." Like CME Express, an independent vendor, Medical World Conference ("MWC"), administered the programs and GSK provided funding. As the name suggests, they were held on Saturday mornings from 9:00 a.m. to 1:00 p.m. Attendance ranged from 125-250 health care professionals. A total of 42 programs were held in different cities throughout the nation over the six-month period. MWC handled all of the administrative functions associated with the conference including printing and mailing invitations several weeks prior to the programs to physicians and other health care professionals who had been identified by MWC. When asked by MWC to do so, GSK sales and marketing personnel would supplement MWC's mailing listing with additional invitees and/or extend invitations directly to health care professionals.

F. Advisory Boards

GSK has two types of advisory boards -- National Advisory Boards and Local Advisory Boards. Advisory boards consist of consultants that advise GSK on strategies for business development, and other commercial issues. GSK may form advisory boards when it has a business need for advice. GSK convenes these boards to provide the Company with an opportunity to periodically discuss significant business needs or issues with expert consultants, physicians, and health care professionals and elicit the advice and expertise of these advisors. GSK uses its National Advisory Boards to receive feedback and advice on clinical trials, product development strategy, new developments in specific disease states, and other nationally relevant issues. Local Advisory Boards provide GSK advice on commercial issues important in a specific region or locality. All consultants are required to enter into a contract prior to serving as an advisory board member.

GSK has established criteria and requirements for its advisory boards which extend to board membership and eligibility; the purpose and scope of board meetings; the process for holding an advisory board meeting; compensation, travel, location of meetings; and entertainment, meals, and gifts. The Company has also established numerous restrictions for its advisory boards. For example, advisory boards are generally not permitted to have more than 20 members. GSK's established policy makes clear that advisory board meetings shall not be used to promote the product to board members.

There are two National Advisory Boards that have been established by the brand team for Wellbutrin – one comprised solely of psychiatrists, and the other comprised of primary care physicians. These National Advisory Boards generally meet no more than twice per year.

GSK, through its field-based Market Development Managers, has established Local Advisory Boards in certain sales regions for the purpose of obtaining specific advice from health care professionals in that locale for Wellbutrin SR and/or issues relating to the therapeutic area of depression. Pursuant to GSK policy, no sales region may have more than two Local Advisory Boards, and no such board may meet more than twice per year. These boards consist of physicians who are selected on the basis of their qualifications and experience. As with National Advisory Boards, these boards are generally comprised of no more than twenty (20) physicians who usually serve at least one year.

Request No. 12

Since October 4, 1996, how many of the physicians who attended a speakers training program on Wellbutrin SR (a) became members of GSK's speaker bureau; (b) actually made at least one presentation on behalf of GSK; or (c) otherwise conducted activities for or on behalf of GSK relating to Wellbutrin SR?

GSK's Response to Request No. 12

During the period January 1, 2001 through October 9, 2002, our records reflect that GSK trained 382 physicians on Wellbutrin SR. Of the 382 trained physicians, 342 (89.5%) joined the Speakers Bureau and made at least one presentation on behalf of GSK relating to Wellbutrin SR.[3]

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[3] Of the 342 physicians who delivered at least one presentation, 16 delivered their presentations *before* receiving speaker training. The remaining 326 physicians delivered presentations *after* speaker training.

The high percentage of GSK-trained speakers who delivered at least one presentation on Wellbutrin SR objectively demonstrates that GSK focuses its training resources and activities on health care professionals it intends to use as speakers. Indeed, the P.R.I.D.E. training program was developed pursuant to a strategic plan to utilize trained physicians to deliver presentations at P.R.I.D.E. speaker events throughout the United States. Below, we provide some additional, specific information about the training and speaking of these health care professionals that you may find useful.

As noted in response to Request No. 1, GSK trained physicians on Wellbutrin SR through two programs – P.R.I.D.E. and regional training conducted by RMS's. GSK held two P.R.I.D.E. speaker training programs. The first occurred January 26 - 28, 2001 (225 attendees); the second occurred on December 6 – 7, 2001 (78 attendees, 37 of whom had not been previously trained). Of the 262 health care professionals trained during the January 2001 and December 2001 P.R.I.D.E. meetings,[4] our records reflect that 249 (95%) made at least one presentation on behalf of GSK relating to Wellbutrin SR prior to October 9, 2002.[5]

Following the December 2001 P.R.I.D.E. program, GSK trained 120 additional health care professionals to be speakers on Wellbutrin SR through RMS's in small-group settings. This training, which is described in greater detail in response to Request Nos. 1 and 14, was developed to address a need to conduct training for physicians who were unable or unwilling to attend the December 2001 training in the wake of the September 11, 2001 terrorist attacks.[6] Of the 120 RMS-trained physicians, 79 (66%) delivered at least one presentation on behalf of GSK relating to Wellbutrin SR between January 1, 2001 and October 9, 2002.[7]

Dr. James Anderson

The following narrative is GSK's response to multiple requests concerning Dr. Anderson, including Request Numbers 2, 4, 5, 6, 7, 8, 9, 10, 13.

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[4] The 41 physicians who attended both P.R.I.D.E. meetings have been counted only once in the 262 total number of physicians trained.

[5] Of the 249 P.R.I.D.E. trained physicians, 2 delivered their presentations before receiving training. The remaining 247 physicians delivered presentations after speaker training.

[6] Prior to October 9, 2002, the RMS's trained a total of 169 health care professionals. That figure represents 120 physicians who had not attended P.R.I.D.E. training either in January 2001 or December 2001, and 49 physicians who had attended one (or both) of the 2001 P.R.I.D.E. programs. The 53 physicians who were trained on more than one occasion have been excluded from the calculations to avoid double-counting.

[7] Of the 79 RMS-trained physicians, 14 delivered their presentations before receiving training. The remaining 65 physicians delivered presentations after speaker training.

A. **Background**

Dr. James Anderson is an endocrinologist and a Professor of Medicine and Clinical Nutrition at the University of Kentucky. In addition to his teaching duties, Dr. Anderson is a practicing physician and researcher.

Dr. Anderson has not received GSK speaker training; he is not a member of GSK's Speakers Bureau; and he is not a member of any GSK advisory committees. GSK has retained Dr. Anderson as a consultant to provide advice on an occasional basis relating to clinical research and obesity to a GSK advisory board committee considering research and development issues. Those consulting activities do not have a promotional component. In addition, Dr. Anderson has engaged in clinical study research funded by GSK relating to bupropion and weight loss. As we describe in greater detail below, he has delivered presentations about that research, however, GSK did not have any involvement in -- or influence or control over -- the content of those presentations.

Please be advised that most of the information presented below is based on interviews with Dr. Anderson, and documents he provided at our request. There is little information in GSK files relating to Dr. Anderson with the exception of the clinical research he performed on behalf of the Company.

B. **Speaking Activities**

During the relevant time period, Dr. Anderson completed a GSK-sponsored clinical study on sustained-release bupropion and weight loss that commenced in 2000. He published an abstract of the study results titled, "Bupropion SR Significantly Enhances Weight Loss When Used with a Moderate-Intensity Lifestyle Intervention." Dr. Anderson presented the six-month data from the study to the 61st Scientific Sessions of the American Diabetes Association ("ADA") in Philadelphia, Pennsylvania, on June 22-26, 2001. The study abstract presented at the conference is attached at Appendix A.

Although GSK provided the funding for the study, it had no involvement in, or influence on the initiation, preparation, development, or publication of the abstract or presentation materials. Dr. Anderson developed both the abstract and the presentation materials. Moreover, Dr. Anderson did not speak on GSK's behalf, nor was any aspect of his presentation promotional in nature. The study abstract materials clearly and properly disclose that the study was supported by a grant from GSK.

This event was nationally advertised and open to all health care professionals attending the ADA conference. The event organizer did not pay the audience to attend or reimburse their expenses. Approximately 100 to 150 physicians, psychiatrists, and other health care professionals attended the event. ADA provides CME credit for the

conference, but ADA did not pay the audience to attend or reimburse their expenses. GSK did not compensate Dr. Anderson for the presentation. GSK reimbursed Dr. Anderson $1,086.44 for out-of-pocket expenses he incurred for presenting the study results. This included his ADA meeting registration fee, travel, and hotel expenses to the June 2001 ADA presentation. GSK is not aware of the creation or availability of any audiotape, videotape, or transcript of the presentation.

On February 26, 2002, Dr. Anderson presented the 12-month data from the same clinical study during the First Annual Nutrition Week: A Scientific and Clinical Forum and Exposition in San Diego, California. Dr. Anderson gave three presentations at the conference, but only one presentation related to bupropion. Dr. Anderson provided us with a copy of the study abstract he delivered at the conference which is attached at Appendix B. The presentation of the 12-month data was sponsored by the American Society for Nutritional Sciences and the American Dietetic Association. GSK did not have any involvement with, or influence on the initiation, preparation, development, or publication of the materials, nor did GSK sponsor the conference. Dr. Anderson did not speak on GSK's behalf, nor was his presentation promotional in nature. GSK did not compensate Dr. Anderson for the presentation. The study abstract materials clearly and properly disclose that the study was supported by a grant from GSK. This event was nationally advertised and open to all nutrition professionals. Approximately 120 physicians, nutritionists, and other health care professionals attended. GSK is not aware of the creation or availability of any audiotape, videotape, or transcript of the event.

On September 18, 2001, Dr. Anderson presented a roundtable dinner discussion for endocrinologists in Lexington, Kentucky. GSK supported the roundtable by paying for the dinner. The topic of the roundtable was: "The Siamese Twins: Diabetes Mellitus and Obesity." Dr. Anderson presented three abstracts during the roundtable:

1. "Lifestyle Intervention Reduces Multiple Risk Factors in Obese Patients With Poorly Controlled Insulin-Requiring Type 2 Diabetes Mellitus;"

2. "Bupropion SR Significantly Enhances Weight Loss When Used With a Moderate-Intensity Lifestyle Intervention" (the same abstract of the six-month data from his clinical trial on Bupropion SR described above); and

3. "Obesity and Disease Management: Effects of Weight Loss on Comorbid Conditions."

Dr. Anderson also showed six related presentation slides, none of which reference bupropion SR or any other prescription drug. A copy of the abstracts Dr. Anderson presented at the roundtable meeting are attached at Appendix C.

GSK did not have any involvement with or influence on the initiation, preparation, development, or publication of the materials presented at the September 2001 roundtable. Dr. Anderson selected the roundtable topic, which was attended by six endocrinologists, three GSK sales representatives, and two GSK sales managers. The physicians were invited to attend by Dr. Anderson. GSK paid for the roundtable dinner, but did not compensate either Dr. Anderson or the attendees. GSK's payment for the dinner was properly disclosed to the attendees. No other pharmaceutical company sponsored the event. The abstracts clearly disclose that the first two studies were supported by GSK research grants. The third study was supported by the HCF Nutrition Foundation, an entity that is not associated with GSK. GSK is not aware of the creation or availability of any audiotape, videotape, or transcript of the event.

Dr. Anderson disclosed to us that he participated in one other program during the relevant period where he discussed bupropion SR -- in conjunction with other drug products -- at a diabetes conference. Importantly, GSK did not have any involvement with, or influence on the initiation, preparation, development, or publication of the materials, nor did GSK sponsor the conference. GSK did not compensate Dr. Anderson for his presentation or reimburse him for his expenses. Based on our discussions with Dr. Anderson, we were able to develop the following additional facts about this presentation, which he titled, "New Recommendations for Nutrition in Patients with Diabetes." He presented this lecture during the Southern Medical Association ("SMA") Fifth Conference on Diabetes: A View of Diabetes, on September 27-29, 2002 in Orlando, Florida.

Dr. Anderson did not speak on GSK's behalf, nor was the event promotional in nature. This event was advertised and open to all members of the Southern Medical Association. Approximately 150 physicians attended. Dr. Anderson received compensation from the SMA to attend and present at the conference. GSK did not provide funding for this program. GSK is not aware of the creation or availability of any audiotape, videotape, or transcript of this presentation.

C. Clinical Research and Consulting Activities

As noted above, Dr. Anderson is not a participant in, or a member of GSK's Speakers Bureau. In addition, Dr. Anderson is not a member of any GSK advisory committees, but he has been retained as a consultant on a couple of occasions to provide research-related advice to a GSK advisory board considering research and development issues.

As noted above, Dr. Anderson has engaged in clinical study research funded by GSK relating to bupropion and weight loss. To formalize the terms and conditions of that research, in February 2000, Dr. Anderson signed an agreement with GSK (GSK North American Medical Affairs) on behalf of the Obesity Research Network ("ORN"), a research organization founded by Dr. Anderson to conduct a multi-site study. The study was formally titled, "24 Week Multicenter Randomized Double-Blind Placebo-Controlled

Parallel Group to Investigate the Efficacy and Tolerability of 300 mg per Day and 400 mg per Day of Bupropion SR Compared to Placebo for the Treatment of Obesity." The 6-month and 12-month results of this study were the basis of the presentations described above. Dr. Anderson served as the clinical investigator responsible for conducting and coordinating research at the six participating institutions. Dr. Anderson's employer, the University of Kentucky, received GSK funding for the study, which provided minor support for his salary.

Dr. Anderson has also received compensation and expense reimbursement for attending clinical investigator meetings as part of his research activities. For example, Dr. Anderson was reimbursed $331.00 for airfare in 2002 for an investigator meeting related to a dose-ranging study for an active ingredient compound under development.

In February 2002, Dr. Anderson's two-year consulting agreement with GSK expired. It has not been renewed. Pursuant to that agreement, Dr. Anderson provided services as needed to support GSK in the "area relating to management of obesity by providing review of [GSK] concept protocols, protocols, and clinical trial data, and strategy for further clinical development of the GW320659 compound for obesity." Dr. Anderson received a payment of $1,500.00 for his consulting services provided during an advisory board committee meeting relating to that specific project. The $1,500.00 payment was for services provided at a meeting related to obesity on February 11-13, 2000 in Arlington, Virginia. Dr. Anderson was also reimbursed $386.00 for related travel expenses.

D. No Involvement with GSK Sales and Marketing Activities

Dr. Anderson has not had any involvement in assisting GSK with respect to sales or marketing of Wellbutrin SR.

E. No Promotional Presentations About Wellbutrin SR

As noted, Dr. Anderson has not attended GSK Speaker Training and is not a member of GSK's Speakers Bureau. GSK has never provided Dr. Anderson with any GSK speaker training material. Moreover, GSK has not provided Dr. Anderson with any promotional materials relating to the actual or potential use of Wellbutrin SR to achieve weight loss or treat obesity.

Dr. Donna Ryan

The following narrative is GSK's response to multiple requests concerning Dr. Ryan, including Requests Numbers 2, 4, 5, 6, 7, 8, 9, 10, 13.

Dr. Ryan has not spoken on GlaxoSmithKline's behalf during the relevant time period, and she is not a member of GSK's Speakers Bureau.[8] Dr. Ryan participated in only one program associated with GlaxoSmithKline since January 2001: a panel presentation at the American Psychiatric Association (APA) Annual Meeting, held in Philadelphia on May 22-23, 2002, and titled, "Chronic Episodic Disorders: Comorbidity & Comprehensive Integrated Treatment." GSK supported this independent Continuing Medical Education program with a $55,000 unrestricted educational grant paid directly to the APA.

Based on our discussions with Dr. Ryan and others associated with the conference, the following is our best understanding and belief of Dr. Ryan's participation in the event. Preliminarily, we note that GSK normally would not possess much of the information we are about to supply since this symposium was an independently-developed CME program. However, GSK has obtained this information in a good faith effort to respond fully to FDA's request.

Dr. Ryan served as a faculty member on a panel for the two-part breakfast symposium and gave an approximately twenty-minute presentation on May 22 titled, "New Developments in Obesity." A copy of the materials presented at the conference, including Dr. Ryan's presentation, is attached at Appendix D. Approximately 320 people attended the event on May 22 and 230 people on May 23, most of whom were psychiatrists. An audiotape of the event and a transcript of the May 22 presentations are attached at Appendix E.[9] This CME event was advertised and open to the public. Non-faculty attendees received Continuing Medical Education credit, but the APA did not pay them to attend or reimburse their expenses.

Dr. Ryan did not speak on GSK's behalf during the conference, nor was the event promotional in nature. The APA approved the topic of the program and the speakers prior to GSK's pledge of an unrestricted educational grant. GSK did not exercise any control over the content of this CME symposium and did not select the speakers. Synergy Communications, a third-party CME coordinator, provided

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[8] In the APA symposium materials, Dr. Ryan is identified, incorrectly, as a member of GSK's Speakers Bureau. Dr. Ryan reported to us that, in an effort to be overly-inclusive, it is her practice to identify her affiliation with companies that supported programs at which she spoke in prior years, including independent CME events. She followed this practice in her commercial disclosures for the APA symposium and included GSK in her list of Speakers Bureaus even though she was not a member. GSK has never paid Dr. Ryan to speak on its behalf.

[9] We requested a copy of the audiotapes from the APA in the course of developing our response to your inquiry, and retained a court reporter to transcribe the May 22 audiotape.

administrative services for the APA symposium, which included coordinating audiovisual materials, advertising and food functions. Synergy invoiced GSK directly for these administrative services.

The APA awarded Dr. Ryan a $500 honorarium for participating in the faculty planning conference call prior to the conference, and a $2,000 travel stipend and $1,500 honorarium for attending and speaking at the event. Like the unrestricted educational grant, GSK paid the cost of the faculty honoraria and related expenses directly to the APA. The APA independently issued the appropriate honoraria to the five faculty members.

GSK did not in any way influence or control Dr. Ryan's presentation or her development of materials presented or distributed at the APA symposium. Many conference attendees completed evaluation questionnaires, a summary of which is attached at Appendix F.[10] The summary demonstrates that of the 258 returned evaluations, approximately 96% of the attendees agreed (agree, moderately agree or strongly agree) that the faculty-presenters both provided unbiased views and covered multiple viewpoints.

In the conference introductions and in materials distributed to attendees, the APA fully disclosed GSK's funding of the conference and its policy requiring each speaker to identify her relevant commercial affiliations. The APA further disclosed GSK's funding in registration materials. Dr. Ryan also disclosed her commercial affiliations at the outset of her presentation. Furthermore, the audience had an opportunity to discuss the speakers' presentations during a substantive question and answer session during the symposium.

Dr. Ryan has not had any involvement in assisting GSK with respect to sales or marketing of Wellbutrin SR during the relevant time period. She is a Professor of Medicine at Louisiana State University and the Associate Executive Director of Clinical Research at Pennington Biomedical Research Center, a research division of LSU that specializes in nutrition and preventative medicine. Dr Ryan has participated as an investigator in clinical studies funded by GSK, including the bupropion weight loss study conducted by Dr. James Anderson (discussed in greater detail in Dr. Anderson's narrative). Pennington Biomedical Research Center was one of the six study locations, with Dr. Ryan serving strictly as a sub-investigator in an on-call capacity for the primary investigators. She was not compensated by GSK for her participation.

Dr. Ryan is not a clinician with an active practice. She has not attended GSK speaker training and is not called on by any GSK sales representative.

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[10] The APA does not retain individual symposium questionnaires after the summary has been compiled.

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The representations made in this response are based on our information and belief. If we become aware of additional or new information that materially alters the accuracy of these responses, we will supplement these responses.

Please note that all materials and information provided in response to your requests and marked "GSK Confidential/Proprietary" are confidential and proprietary to GSK, and as such, are protected under the applicable provisions of 18 U.S.C. 1905 or 21 U.S.C., Section 331(j), and all accompanying regulations. Additionally, GSK is providing all information and documents to the Division of Drug Marketing, Advertising and Communications for its use during this inquiry only.

Sincerely,

Lauren C. Stevens
Vice President and
Associate General Counsel
US Legal Operations

Enclosures: Appendices A through F

3/28/2003

GlaxoSmithKline

Cover Letter Via Facsimile Transmission (301) 594-6771
Followed By Airborne Express with Attachments

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March 28, 2003

Lesley R. Frank, Ph.D., J.D.
Regulatory Counsel
Food and Drug Administration
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Re: NDA 20-358
Wellbutrin SR® (bupropion HCl) Sustained-Release Tablets
MACMIS #11170

Dear Dr. Frank:

This letter represents a supplemental response to your letter dated October 9, 2002, concerning Wellbutrin SR (bupropion HCl) Sustained-Release Tablets. We are providing information and documentation responsive to Request Numbers 3, 7 and 8.

Consistent with our prior agreement, reflected in our letter of October 29, 2002, the information provided herein and responsive to your requests covers the period January 1, 2001 through October 9, 2002. We refer to this period below as the "relevant time period."

GSK's Response to Request Nos. 3, 7 and 8

The following responds to FDA's requests for information about GSK-sponsored speaker events related to Wellbutrin SR, including Request Numbers 3, 7, and 8. In addition, we are providing copies of GSK's P.R.I.D.E. Speaker Event Spreadsheet ("P.R.I.D.E. Spreadsheet") and GSK's Wellbutrin SR Speaker Event Spreadsheet ("Event Spreadsheet"), which provide details about GSK-sponsored speaker events during the relevant time period. We note that GSK specifically created these spreadsheets in response to FDA's request for information. The information collected in these spreadsheets derives from a variety of GSK programs and did not exist in this format prior to FDA's request for information.

A. P.R.I.D.E. Program Speaker Event Spreadsheet

In 2001 and 2002, GSK sponsored approximately 2650 P.R.I.D.E. speaker events. During this time period, GSK employed approximately 1250 sales representatives with at least partial responsibility for Wellbutrin SR. GSK's vendor, SCS Healthcare Marketing, Inc., assembled a P.R.I.D.E. Spreadsheet at our request that reflects the date, location, speaker name, and number of attendees for each P.R.I.D.E. speaker event. A copy of the P.R.I.D.E. Spreadsheet is attached at Appendix A. The "Attendees" field in the P.R.I.D.E. Spreadsheet is blank in cases where SCS and GSK do not have information identifying the number of persons who attended those events. Additional details about the P.R.I.D.E. speaker events were previously provided by GSK in response to Request No. 1.

B. Wellbutrin SR Speaker Event Spreadsheet

In 2001 and 2002, GSK sponsored approximately 5850 speaker events that were identified as being related to Wellbutrin SR. As discussed in GSK's response to Request No. 1, these speaker events are not part of the P.R.I.D.E. program speaker events; they are additional speaking events that occurred during the relevant time period. GSK assembled a spreadsheet that reflects the GSK program reference number, speaker name, date, location, topic, and number of attendees for each GSK-sponsored Wellbutrin SR speaker event. A copy of the Event Spreadsheet is attached at Appendix B. GSK sales representatives were responsible for entering this detailed information about speaker events directly into GSK's system. The "Attendees" field is blank in cases where GSK does not have information identifying the number of persons who attended those events.

The speakers at these events are health care professionals, usually physicians, who are members of GSK's Speakers Bureau. GSK generally sponsored and paid for the events, which typically occurred in a lunch or dinner setting. GSK's funding of the event and relationship with the speaker typically would have been disclosed to the audience at the time of each event or in the invitation to the event.

The events usually were attended by health care professionals (e.g., primary care physicians and psychiatrists), who generally were invited by GSK sales representatives. GSK sales representatives selected the attendees based on health care professionals in their territories who may have been interested in the topic. Attendees were not paid, reimbursed, or otherwise compensated to attend these events, with the exception of reimbursement for parking fees in some cases.

You will notice that titles for a small fraction of the total speaker events included issues, phrases, or uses that could be outside the approved indication for the product. More specifically, we discovered that topics for approximately 75 of the 8,500 P.R.I.D.E. and Speaker Events -- less than 1 percent -- include terms or uses that could be outside the approved indication for Wellbutrin SR. GSK has taken action to ensure that future presentation topics are within the approved product indication, as discussed below.

We emphasize that we have not independently verified or confirmed that the product was discussed or promoted, either directly or indirectly, for an unapproved use during these events. A given presentation may have been disease-awareness in nature, not product specific; other presentations may have involved multiple products with little or no discussion of Wellbutrin SR with respect to the topic chosen. Further, we cannot confirm whether the topic was selected by a GSK sales representative because health care providers also chose topics. We are bringing this to your attention in a good-faith effort to be responsive to your information request and to capture even potential instances of topics that may not be consistent with the approved indication for Wellbutrin SR or the manner in which the company promotes the product. After becoming aware of these presentation topics, GSK undertook measures to prevent future presentations involving Wellbutrin SR from reflecting terms or uses that could be outside the approved indication. Specifically, GSK is in the process of developing 20 to 40 approved presentation topics from which GSK sales representatives must select from a database. In addition, GSK thoroughly reviewed its speaker presentation policy, including the selection of topic and content, with each sales representative associated with a topic potentially relating to an unapproved indication.

These titles are isolated and infrequent examples -- less than 1 percent of over 8,500 events -- and are not representative of the topics on the spreadsheets. The vast majority of these events took place in 2001 -- less than 10 occurred in 2002. We believe that the relatively few and declining number of these events, along with the additional controls we are implementing, demonstrate GSK's ongoing commitment to promote Wellbutrin SR for a use that is consistent with product labeling.

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The representations made in this response are based on our information and belief. If we become aware of additional or new information that materially alters the accuracy of these responses, we will supplement these responses.

Please note that all materials and information provided in response to your requests and marked "GSK Confidential/Proprietary" are confidential and proprietary to GSK, and as such, are protected under the applicable provisions of 18 U.S.C. 1905 or 21 U.S.C., Section 331(j), and all accompanying regulations. Additionally, GSK is providing all information and documents to the Division of Drug Marketing, Advertising and Communications for its use during this inquiry only.

Sincerely,

Lauren C. Stevens
Vice President and
Associate General Counsel
US Legal Operations

Enclosures: Appendices A and B

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